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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/340,690	06/29/99	NI J	1488.0770007

HM22/1004
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EXAMINER	
DRAPER,G	
ART UNIT	PAPER NUMBER
1647	8

DATE MAILED: 10/04/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 27-174 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 27-174 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 27-174 were ~~are~~ subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3 different nos

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

PTOL-326 (Rev. 10/95)

* US GPO: 1996-409-290/40026

1. **Part III: Detailed Office Action**

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647.

2. ***Formal Matters:***

While the claims are not indefinite for failing to set forth the name of the protein, it is suggested that the name of the protein be insert so that the inventive concept can be clearly identified by the claims, and this would aid in "search"-particularly since many of the applications by the Assignee merely recite a Seq ID to identify their claimed protein. The following is suggested: "An isolated Human Tumor Necrosis Factor Receptor-Like 2 polypeptide comprising....."

3. ***Restriction Requirement:***

All of the claims are directed to protein and/or composition, so no restriction is required. Accordingly, this office action is directed to the merits of claims 27-174--all of the claims of record.

4. ***Objections and 35 USC 112 Rejections and 101 Rejections:***

4a. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-174 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention..

The claims appear to be consistent with the CCPA's position set forth in In re Chandler, 254 F.2d 396, 117 USPQ 361 (1959) and In re Chandler, 319 F.2d 211, 225, 135 USPQ 138, 148 (1963) where it was held that applicant's latitude in stating their claims in regard to number and phraseology employed "should not be extended to sanction that degree of repetition and multiplicity which beclouds definition in a maze of confusion"). Furthermore, such claims, or claim limitations or permutations could be rejected one over the other if they differ only by subject

matter old in the art (*Ex parte Whitelaw*, 1915 C.D. 18, 219 O.G. 1237 (Comm'r Pat. 1914), where this doctrine is applied when the claims are unduly multiplied or are substantial duplicates (*Ex parte Kochan*, 131 USPQ 204, 206 (Bd. App. 1961).

Claims 170-176 are confusing in the limitation for the first and second polynucleotide, and/or these claims are also confusing or not enabled for the limitation of the claim that the protein will hybridize to the complement, because the complement can not encode for the protein.

4b. 101 Rejection:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69-80, 141-169 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility and/or because the disclosed invention is inoperative and therefore lacks utility.

Claims 69-80, 141-169 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 69-80, 141-169 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The various small protein fragments/portions of the claims are not enabled by the specification's teachings and therefore fail to have a specific utility (see the comments below)

4c. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and

process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-44, 51-56, 63-80, 87-174 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human tumor necrosis factor receptor-like 2, and a limited number of modified proteins forms, does not reasonably provide enablement for: a) any fragments, portions, partial sequence and/or antigenic regions or 30-50 contiguous regions (cl=39-44, 51-56, 63-80, 87-92, 141-169); c) any sequences that are at least 95% identical to those of the various Seq ID (claims 93-140); d) does not provide enablement complementary sequence to encode for the protein; e) nor is there enablement for the fusion of any heterologous sequence to the protein (cl=30, 36, 42, 48, 54, etc and all claims which recite this). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success the invention commensurate in scope with these claims.

First of all, the some of the claims appear to rely on the use of a novel deposit, but applicants have not provided all of the required averments for deposited material (See MPEP Chapter 2300), and are thus, non-enabling for such. A copy of the contract is requested.

While it is well settled that a specification need not contain examples in order to be enabling, in the express absence of such, the specification must provide enablement alternatively in the form of evidence or guidance. It is also known and accepted that examples, evidence of guidance are not required if, on its face, it is clear to the skilled artisan that the claims are enabled; and when there is no reason to question the objective truths of applicant's mere statement or assertions that the claims are enabling for various proteins or modified forms that is at least 95% identical to a amino acid sequence for the protein of the various Seq ID that are properly with the scope of the claims. However, in addition to there being insufficient examples, the specification is also devoid of sufficient evidence or guidance that would serve to enable this aspect of the claims. The following discussion will serve to establish the Examiner's position for questioning the objective truth of applicant's mere statements, and consequently show that these claim limitations

are not enabled by the specification.

Besides the mere statements about what is intended and/or encompassed by the use of percent identity, the only other information provided is general reference to hybridization, protein fragments, epitope-bearing portions, and modifications for the encoded protein which has been presented by way of general teaching references that appear to merely represent "boiler plate" teaching for how to achieve such modifications. It is not clear where these different regions are and if they are merely at conservative sites or at other structurally or functionally relevant sites. The specification has not disclosed structure/function studies for the encoded protein so that the skilled artisan would know where sensitive regions are such as folding or binding regions, or regions where the activity resides for enzymatic or thermally sensitive regions, and this is particularly relevant since most of the claims define the nucleic acids in terms of the encoded protein. In the absence of such, it would entail undue experimentation for the artisan to go about picking and choosing regions that can be modified with a reasonable assurance that the resulting protein will possess the desired activity.

Although some of the claims set forth specific amino acids or ranges from the mature protein, there is insufficient teachings in the specification that each of these regions are biologically active or encompasses regions on the protein where various other activities for the protein reside. The specification has set forth generic definitions for "polypeptides", variants and modifications, but beyond this, there is no other enablement nor specific structure/function studies, or guidance for which regions are important for the various structural and functional characteristics that are associated with the polynucleotide and the encoded protein; and which can tolerate changes for the desired uses. In the absence of such teachings, the skilled artisan would be faced with undue experimentation for practicing the scope of the claimed invention. The mere recitation of procedures and citations for making modification and fragments does not satisfy the enablement for such broad claims, because it fails to establish a nexus for making the various determinations desired for the polynucleotide and encode protein of the invention with a reasonable assurance that the resulting modified product will possess the desired

properties/characteristics. Although applicants have speculated that the encoded protein is related to other known TNF family of receptors, there does not appear to be disclosed a sufficiently reproducible method for determining the desired activity that would be associated with the various permutations within the scope of the claims. Accordingly, the specification has not enabled the breadth of the claims.

Several of the rejected claims are directed to specific fragments, parts, or contiguous , contiguous portions, thus, the basis for the lack of enablement for these claims are similar and/or related to the utility rejection, and therefore will be addressed together, especially for fragments and contiguous sequences, based on the fact that the specification has not provided sufficient enablement in the form of examples, evidence or guidance for the entire scope of these claims. The claims are not enabling for **any** fragment of the protein, irrespective of whether it is an antigenic fragment, epitope, parts or portions thereof or contiguous amino acid residues. The specification makes general reference to fragments (presumably from proteolytic cleavage or chemical synthesis); however, this does not serve to enable the scope of the claims. Enablement for the claims can not merely be perfected by the general reference to cleaving the protein from one or both ends to obtain biologically protein fragments. There must be some guidance, the establishment of a nexus or a reasonable degree of predictability about where these regions are and how to obtain fragments or contiguous region of sufficient size that could be used for their intended purpose.

Applicants can not merely rely on the issue of "make and test" to satisfy the enablement provisions for the breadth of the fragments of substitutions presented in the claims. Rather, the skilled artisan would need to know more than just how to make the fragment from cleavage, but the artisan would need to necessarily know how to make the specific fragment with reasonable assurance that the various fragments would possess the desired activity and can be usable as such. Furthermore, there are little or no structure/function studies provided of record for the protein, thus, the skilled artisan does not know where the binding regions are; nor is it clear where usable epitopic/ antigenic regions are; where the thermal, enzymatic or other stability regions are; if all or

part of the N-and C-terminals are necessary. Since there is insufficient enablement for where the biologically active regions are, it would be difficult to determine what specific functional activity on the protein these fragments cover since many protein possess multiple biological activities, thus, the activity that the fragment(s) have to possess has not been set forth in the claims, nor enabled by the specification. All of these variables would have to be known for the skilled artisan to produce fragments that possess the desired properties and therefore be usable in a manner contemplated. Without such information, the skilled artisan would have to resort to trial-and-error and be faced with undue experimentation for making and using the full scope of these fragments based on the limited characterization set forth in the specification, as well as the limited characterization that has been set forth in the claims for the fragments.

The specification still does not provide enablement for such because the there are no teachings for what region on the protein this activity corresponds to; and applicants have merely provided a definition for "fragment" and recited very general and non-specific way of obtaining the fragments, thus, based on all of the other reasons set forth above, the artisan would encounter undue experimentation in order to practice the scope of these claims. In the absence of specific examples, in order to satisfy the enablement provision to support the scope of the claims, alternatively, applicants should provide evidence and/or guidance to enable the scope of these fragments. However, the specification also fails to provide the necessary evidence or guidance the enable the scope of the claims. Therefore, the skilled artisan would be faced with undue experimentation for trying to determiner how and where to start in order to make the full scope of the claims, because to enable the claims it does not merely require cleaving the protein from one or both ends to produce the various fragments or part/portions and this is true for fragments that are claimed as biologically-active fragments where no specific activity is identified. There must be some guidance or a reasonable degree of predictability about where these regions are and how to obtain a fragment of sufficient size that could be used for its intended purpose.

Even though in Figure 3, applicants attempt to provide the analysis of the protein for such things as antigenic index (via Jameson-Wolf), α and β turns/regions (via Garnier-Pobson,

Chou-Fasman or Eisenburg); coil regions; hydrophilic, hydrophobic and amphipathic regions (via Kyte-Doolittle, Hopp-Woods or Eisenberg); flexible region (via Karplus-Schulz); surface probability (via Emini), and antigenic or epitopic regions-all via a computer program that does not expressly state the exact residue location, but rather merely estimate on these regions. Antigenic Index or Jameson-Wolf graph, presumably identify epitopic regions and in the brief description for this figures, applicants have listed peptide regions that they conclude are highly antigenic; however, a review of this figure and other statements in the specification does not make clear that the antigenic regions are for any specific amino acid residues, especially those that may be listed in the claims, because these teachings are not sufficiently precise enough to draw such conclusions that would satisfy the enablement provisions of the statue. In the absence of this, the specification has not provided sufficient evidence or examples or guidance to ensure that these regions are antigenic and that antibodies could be specifically elicited to these peptides. It is well known in the art that antibodies that bind to the full length protein possess different and distinct structural and functional characteristic from antibodies that bind to only certain portions of a protein's structure. Furthermore, it is also known that all small peptide portions do not elicit an antibody response and the affinity and specificity of binding depends on the size and make-up of the antigenic peptide. Thus, the use of one peptide regions of a given size does not necessarily predict that all other peptides derived from that protein can also bind to an antibody or elicit an antibody response. In the absence such, the specification has not provided sufficient evidence or examples or guidance to ensure that these regions are even antigenic in nature and sufficient to elicit an antibodies response.

While it well settled that a specification need not contain examples in order to be enabling, however, in the express absence of such, the specification must provide enablement alternatively in the form of evidence or guidance. It is also known and accepted that examples, evidence or guidance are not required if, on its face, it is clear to the skilled artisan that the claims are enabled; and when there is no reason to question the objective truths of applicant's mere statement or assertions that the various protein fragments or contiguous regions are active or enabled by the

specification. But, in addition to there being insufficient examples, the specification is also devoid of sufficient evidence or guidance that would serve to enable the claims. For example, at various pages of the specification applicant(s) have merely set forth general statements about variants, polypeptides and modifications, fragmentation, biological activity of the full length protein; and have cited general teaching references that appear to merely represent "boiler plate" teachings for how to achieve such modifications. However, what is not taught is the nexus, relationship or predictability that these general teachings would have to the various fragments parts/portions or contiguous amino acids and even the various modified amino acid residues they relate to the resulting functionality of the claimed products and the enablement of such.

Furthermore, the specifications does not provide enablement for such because the there are no teachings for what region on the protein the activity corresponds to and if the areas where the functional activity resides covers all or part of the 5% difference as recited in the claim; or the 1-30, or 1-50 contiguous regions of the claims. Applicants can not merely rely on the issue of "make and test" to satisfy the enablement provisions for the breadth of the various modifications that would represent the 5% difference in the protein's sequence as recited by the claims. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structural/ functional relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding, stability, or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for sites which represent other characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity or other functional/biologically active residues or regions. In many instances, many of the regions can tolerate only relatively conservative substitutions or no substitutions.

Therefore, the claim is not enabled for the vast number of changes the is encompassed by the 95% limitation of the claim,, nor the specifically recited fragments.

In view of all of the above, the skilled artisan would encounter undue experimentation to achieve the scope of these claims, because there also does there appear to be a sufficiently established and reproducible assay for determining the biological activity that applicants desire to be associated with the protein fragments or contiguous regions.

The specification is also non-enabling for any heterologous sequence fused the nucleic acid that encodes for the mature protein or portions thereof, as in the claims. The scope of this term encompasses nucleic acid sequences that do not encode for protein as well as nucleic acids where the sequence is responsible for expression of the protein. The nature and make-up of these heterologous sequence bears an importance on the expression and functionality of the encoded protein products, thus, without sufficient examples and guidance for the need of this heterologous sequence, the artisan would again be faced with undue experimentation for selection a sequence that would work in conjunction with the structure and function of nucleic acid sequence and the encoded protein sequence. Heterologous sequence or protein represent a broad category, such that a lack of guidance for the appropriate sequence that could function in a manner desired by the claims would have to be set forth in the specification in order to enable the scope of the claims.

6. Prior Art Rejections:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 69-80, 141-169, 170-176-claims to non-specific fragments and hybridizable sequences, are rejected under 35 U.S.C. 102, or in the alternative under 35 USC 103 as being anticipated or obvious over applicants' admission at pages 1, 8 and figure 16 that the instant TR2 has "considerable homology to murine CD40". Based on these admission and the non-stringent hybridization condition of these claims, the prior art would appear to anticipate the claims.

9. Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to **Garnette D. Draper, Art Unit 1647, whose telephone number is (703) 308-4232.** Examiner Draper can normally be reached Monday through Friday, 9:30 A.M. to 6:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

GARNETTE D. DRAPER
PRIMARY EXAMINER
GROUP 1800